UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,562	11/14/2001	Avi J. Ashkenazi	P2730P1C18	2836

35489 7590 07/01/2004

HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CO 94025-3506

EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,562	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/24/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Part III: Detailed Office Action

Claims 119-124 are pending and under consideration.

The claims are drawn to anti-PRO1111 (SEQ ID NO: 229) polypeptide antibodies.

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

IDS:

The information disclosure statement, filed 5/24/2002, has been considered. The BLAST results demonstrate that applicants are aware of nucleic acids with identity/homology to the one claimed herein. However, as the BLAST results do not give sufficient identifying information, the Examiner cannot determine if said sequences constitute prior art.

Priority Determination:

The utility for the claimed protein is activity in a chondrocyte redifferentiation assay, which confers utility to the claimed antibodies. The earliest disclosure of this result that can be confirmed by the Examiner is in US Application 09/941992, filed 8/28/01. It is suspected that priority may exist in PCT/US00/08439. Applicants are requested to provide a copy of that portion of the PCT application that contains the chondrocyte redifferentiation assay in response to this office action to allow a proper priority determination. Accordingly, priority is set at 8/28/2001, with possible priority to 3/3/00, pending review of the PCT application.

It is further noted that applicants may argue that the results of the assay beginning at page 546 of the specification, the delta Ct assay, establish utility and enablement for the claimed invention, resulting in an earlier priority date. That assay is not found to be enabling as required by 35 U.S.C. §112, first paragraph. The results indicate a *mild* amplification in fewer than half the Lung adenocarcinoma, lung squamous cell carcinoma, and colon adenocarcinoma cell lines studied. PRO1111 was found to be amplified approximately two-three fold in 6 of 12 human

lung tumor squamous cell carcinoma cell lines, 4 of 11 human lung tumor adenocarcinoma cell lines, and 4 of 17 colon adenocarcinoma cell lines. The finding that the nucleic acid encoding PRO1111 is amplified, likely indicating aneuploidy, in the aforementioned tumor types is insufficient to confer utility or enablement to the nucleic acid. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. In this case, the sequence of PRO1111 was found at no more than three copies per cell, and only in a minority of tumors tested. The person of ordinary skill in the art would not consider the results to be significant or diagnostic in view of the review by Sen. Further, a search of the art has revealed that J. Wang et al. have reported that the protein encoded by SEQ ID NO: 228 is *downregulated* in brain tumor (see search results for us-09-989-2749-229.rspt, result 1, enclosed). Accordingly, it is not clear whether or not PRO1111 is diagnostic of cancer, or if so which cancers, and the specification does not enable the use of PRO1111 for such diagnosis, and the result from the amplification assay cannot be relied upon to establish a priority date for the nucleic acid. With respect to the claimed protein, even *if* the amplification assay demonstrated utility and enablement of the nucleic acid, it would not do so for the claimed protein. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Thus, the data do not support the implicit assertion that PRO1111 can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to determine whether PRO1111 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial.

The Examiner's position that an increase in nucleic acid copy number is not predictive of a similar association for protein is supported by the prior art. The art does not recognize that protein levels are increased when gene amplification occurs. For example, Pennica et al., teach that WISP1 and WISP2 are both amplified in tumors, but RNA expression of WISP2 was *reduced* in 79% of tumors, while that of WISP1 was *increased* in 84% of tumors (see abstract). See also Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein

expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Finally, see Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, the art indicates that it is not the norm that gene amplification, or increased transcription, results in increased protein levels. Accordingly, the showing that the DNA encoding PRO1111 is present in increased copy number in a particular tumor type would not be sufficient to establish any utility for the protein encoded thereby or antibody that binds to the protein.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to the date recited above which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to that date.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 119-124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 119 states that the claimed antibody "binds" the protein of SEQ ID NO: 229, whereas dependent claim 124 states that the antibody "specifically binds". The term "specifically" in claim 124 is a relative term that renders the claim indefinite. The term "specifically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably

apprised of the scope of the invention. Further, the use of the term in the dependent claim raises the issue that the antibodies of the other claims may *not* be specific to the protein, in which case the metes and bounds of the claims are in question.

Claim 122 is further indefinite as an antibody cannot be a fragment of itself.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

Priority is set at 8/28/2001, but may be granted to 3/3/00. Accordingly, the rejections below are being set forth with each possible priority date in mind.

A search of the nucleic acid sequence databases revealed the following prior art:

Reference	Date	Author	Identity to SEQ ID NO:228
AI769814	12/21/99	NCI-CGAP	100% to bases 1703-2180
AI435407	3/30/99	NCI-CGAP	99.8% to bases 1743-2185
AI470931	4/13/99	NCI-CGAP	100% to bases 1795-2179
T15752	7/25/96	R. Berry et al.	100% to bases 1870-2184
U.S. Patent Number 6,689,866, SEQ ID NO: 9	3/8/00	Shimkets	99.7% to bases 1-2183
U.S. Patent Number 6,689,866, SEQ ID NO: 31	3/8/00	Shimkets	Encodes XC domain, 100% identity to SEQ ID NO : 229, residues 45-492.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 119-122, and 124 are rejected under 35 U.S.C. 102(a) or (b) as being anticipated by Jacobs, WO 99/50405. SEQ ID NO: 2 of the publication is 99.7% identical to SEQ ID NO: 229 of the instant application. Antibodies are disclosed beginning at page 77, and include monoclonal, polyclonal, humanized, chimeric, and single chain antibodies. At page 78 the disclosure states that the antibodies may be used for detection of protein. Accordingly, the claims are anticipated by Jacobs.

Claims 119-124 are rejected under 35 U.S.C. 102(e) as being anticipated by Shimkets, U.S. Patent Number 6,689,866 or US Patent Application Publication US2003/0054514 A1, or US Patent Application Publication US2003/0003532 A1. The US Patent Application Publications are divisionals of the patent, and differ only in the claims. The '514 publication contains claims to nucleic acids, proteins (see claim 11), and antibodies (see claim 13), and the '532 application contains claims to nucleic acids and vectors. The teachings will be discussed with reference to the issued patent. SEQ ID NO: 9 of the patent is 99.7% identical to SEQ ID NO: 228 of the instant application, at bases 1-2183 (bases 159-2341 of the patent), and encodes a protein 99.2% identical to that of SEQ ID NO: 229. SEQ ID NO: 31 is a fragment of SEQ ID NO: 9, is identified as encoding the extracellular domain (see figures 17A and 17B), which is 100% identical to residues 45-495 of SEQ ID NO: 229. Antibodies are disclosed at column 36, and include monoclonal, polyclonal, humanized, chimeric, and single chain antibodies. Labeled antibodies are disclosed at column 37, lines 44-45. Accordingly, the claims are anticipated by Shimkets.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 119-120 and 123-124 are rejected under 35 U.S.C. 103(a) as being obvious over any one of Loci AI769814, AI435407 , AI470931, or T15752, in view of Sibson et al.

The teachings of the primary references are summarized in the Table above. Each has over 99% identity to SEQ ID NO: 228 over the full length of the locus from the database. As sequence identity is calculated relative to the shorter of the two sequences being compared, the proteins encoded by the sequences would meet the limitations of claims 119-123.

Sibson et al. disclose that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such cDNA's. See pages 8-13. Antibodies, including monoclonal and polyclonal antibodies are disclosed at the paragraph bridging pages 8-9. At page 12, it is disclosed that the antibodies "can be used for localizing in situ, or quantifying in sample through, for example, ELISA or RIA assays", and goes on to disclose use in *in vivo* imaging. The person of ordinary skill in the art would immediately grasp such as a disclosure of labeled antibodies.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the DNA's disclosed by any one of the primary references to express and then isolate the encoded polypeptide and make monoclonal, polyclonal and/or labeled antibodies as taught by Sibson et al. in view of Sibson et al.'s suggestion that it would be desirable to do so, as cited above.

Claims 121-122 are rejected under 35 U.S.C. 103(a) as being obvious over any one of Loci AI769814, AI435407 , AI470931, or T15752, in view of Sibson et al. and further in view of U.S. Patent Number 5,565,332 (Hoogenboom et al.) in the case of claim 121, or in view of U.S. Patent Number 4,946,778 (Ladner et al.) in the case of claim 122.

Claims 121-122 contain the additional limitation that the claimed antibodies are humanized, or a fragment of an antibody. The primary references taken in view of Sibson teach antibodies, monoclonal antibodies and labeled antibodies, but not humanized or fragment antibodies.

Hoogenboom et al. disclose humanized antibodies and methods of making such. At col. 1 lines 16-30 they disclose the advantages of such as being overcoming the problem of elicitation of anti-globulin response when a non-human antibody is administered to a human. See also col. 3 lines 8-15 in this regard. At column 2 lines 57+, they disclose that antibody fragments can perform the function of whole antibodies, and set forth single chain antibodies as being examples of antibody fragments.

Ladner et al. teach the construction of single chain antibodies. The stated advantages of such as enumerated at column 3 lines 32-48 include smaller size, greater stability, lower cost, lower immunogenicity, etc.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the antibodies of obvious over the Hillier disclosures in view of Sibson into the single chain or humanized antibodies of Ladner et al. or Hoogenboom et al. to attain the known and expected advantages of such as set forth by the secondary references and as referred to above. It is noted that a single chain antibody is considered additionally to be an 'antibody fragment', as disclosed by Hoogenboom et al.

Accordingly, the invention, in view of the prior art, is *prima facie* obvious.

Claim 123 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobs, WO 99/50405 as applied to claims 120-122 and 124 above.

Claim 123 differs from the disclosure of Jacobs in specifying that the claimed antibody is labeled. However, the production of labeled antibodies is considered obvious over Jacobs, as the practice of labeling antibodies to allow detection of such are notoriously old and well known in the art, and would be immediately envisaged by the person of ordinary skill in the art upon reading the Jacobs et al. disclosure, in view of the disclosure of Jacobs that the antibodies may be used for detection of protein.

Advisory Information:

No claim is allowed.

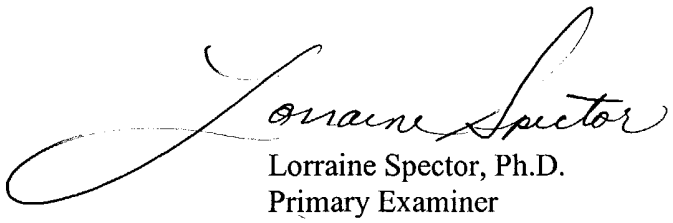
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number is 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz. ***Effective 1/21/2004, Dr. Kunz' telephone number is 571-272-0887.***

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.
Primary Examiner